REMARKS/ARGUMENTS

Claims 1 and 40 have been amended to recite a hindered base capable of effecting acyl migration. Applicants respectfully submit no new matter has been introduced by these amendments. Claims 1-43 are pending.

Rejections Under 35 U.S.C. §112

Claims 1-43 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The Examiner argues there are many hindered bases and Applicant should be required to include specific bases in the claims. The Examiner further argues there are no specific examples in the specification to limit the definition of a hindered base. Applicants traverse this rejection.

Breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). Applicants respectfully submit the Examiner's position has no basis in the art and rather improperly seeks to narrow claims of proper breadth. In particular, Applicants submit the term "hindered base" is completely understood within the art without the need for reference to specific bases. Additionally, Applicants strongly disagree with the suggestion that specific bases must be included in the claims to be definite. Rather, Applicants respectfully submit that in making the present rejection, the Examiner has failed to recognize that the patent literature itself clearly accepts the term "hindered base" as self-supporting.

To this end, Applicants respectfully direct the Examiner's attention to U.S. Patent No. 7,022,852. Claim 4 of the '852 patent recites a process for preparing a compound wherein step (a) comprises reacting a starting compound with a sterically hindered base. The specification of the '852 patent only describes the hindered base in terms of a preferred embodiment (column 3, lines 20-21) and disclosing that alkali metal salts of bulky alcohols or amines are suitable bases (column 7, lines 63-67).

Similarly, Applicants point to U.S. Patent No. 7,018,784. Therein, claim 13 recites that a previously claimed additive can be a sterically hindered base. In the specification, the '784 patent only describes sterically hindered bases as compounds suitable for acting as catalysts, and exemplifies such bases as trioctylamine or tertiary amines, diazabicycloundecene,

diazabicyclononene, and diazabicyclooctane (see column 10, lines 37-44). Applicants were quickly able to find numerous further issued patents broadly claiming hindered bases without reciting specific bases. See, for example, U.S. Patent No. 6,960,654; U.S. Patent No. 6,207,829; U.S. Patent No. 6,140,515; U.S. Patent No. 6,025,519; and U.S. Patent No. 5,472,880. In all of these cases, the term "hindered base" was found sufficiently definite to stand alone in issued claims.

Applicants respectfully submit the above examples clearly indicate the term "hindered base" is well understood in the patent literature such that upon seeing the term, a skilled artisan can immediately recognize what is meant thereby. Nevertheless, in the present case, a skilled artisan is not required to only rely on the knowledge in the art. Rather, the present application clearly describes what is meant by the term.

Claim 1 recites the step of treating a primary amine compound with a hindered base capable of effecting acyl migration to form another taxane molecule. Applicants submit this language clearly describes the hindered bases being claimed. Page 4 (first paragraph) of the specification likewise discloses that the base used in the inventive method is a base that can effect acyl migration. Triaklylamines, such as triethylamine, are disclosed in the fourth paragraph of page 4 as preferred bases for effecting acyl migration. Still further, at the bottom of page 21, the specification discloses that any base known in the art to facilitate acyl migration may be used provided it does not adversely affect other functionality present on the taxane molecule or produce by-products. The specification goes on to disclose at the top of page 22 multiple examples of bases suitable for effecting acyl migration (*e.g.*, trialkyamines, pyridines, substituted pyridines, sodium bicarbonate, sodium carbonate, and potassium carbonate).

In light of the above, Applicants respectfully submit the term "hindered base" is well-known in the art, and the patent literature indicates use of the term in a claim provides proper breadth to the claim without being indefinite. Moreover, the present claims recite hindered bases capable of effecting acyl migration, and the present specification provides ample disclosure regarding the action of acyl migration and the types of hindered bases expected to effect such migration. Accordingly, Applicants submit the claims are not indefinite, and Applicants respectfully request reconsideration and withdrawal of the present rejection.

Claims 1-43 also stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking sufficient written description to illustrate possession of the claimed invention. Particularly, the Examiner argues the specification lacks information to limit the definition of a hindered base. Applicants respectfully traverse this rejection.

As previously pointed out, the term "hindered base" is well understood in the art and is broadly recognized in the patent literature. As noted above, the present claims recite hindered bases capable of effecting acyl migration. Such bases are described in the specification at page 4 (first and fourth paragraphs) and in the paragraph bridging pages 21 and 22. Moreover, at the top of page 25, the use of triethylamine (a hindered base) is exemplified as effecting benzoyl migration.

In light of the above, Applicants respectfully submit the present specification provides ample description of the hindered bases for effecting acyl migration, as claimed. Moreover, as the term "hindered base" is so clearly accepted and understood in the relevant art and the patent literature, Applicants submit the skilled artisan would immediately recognize what is meant by the term. The noted written description, particularly when combined with the recognition in the art, clearly indicates a skilled artisan, viewing the present application, would clearly recognize the inventors were in possession of the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

Rejections Under 35 U.S.C. §101 and §112

Claims 1-43 stand rejected under 35 U.S.C. §102 and §112, first paragraph, as allegedly being inoperable. The Examiner particularly alleges there is a missing step for deprotecting the OH group in the C2' position. Applicants respectfully traverse this rejection.

In alleging the absence of a deprotecting step, the Examiner is attempting to impose a reaction step not required according to the present invention. Claim 1 recites a method of converting a taxane molecule according to a defined formula, wherein C2' has an acyl group attached thereto and C3' has an amide group attached thereto. The method comprises: (a) reductively deoxygenating the C3' amide group to form a C3' imine; (b) hydrolyzing the C3' imine to form a C3' amine; and (c) treating the compound with a hindered base capable of effecting acyl migration. This forms another taxane molecule having a C2' OH and a C3' amide.

In the final step of the claimed method, the C2' acyl group migrates (*i.e.*, is transferred) to C3', and the acyl group is replaced at C2' with an OH group. There is no need to deprotect the OH group because it merely replaces the migratory acyl group. Further, as noted above, the migration of the acyl group from C2' to C3' is effected by the addition of the hindered base. Accordingly, Applicants respectfully submit the present claims fully recite the necessary method steps and the specification fully describes such steps. Thus, Applicants respectfully request reconsideration and withdrawal of the present rejections.

Rejections Under 35 U.S.C. §102

Claim 40 stands rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,679,807. Applicants respectfully traverse this rejection.

Claim 40 recites a method of converting an acyl-protected taxane molecule comprising: (a) reductively deoxygenating an amide group on the taxane molecule to form an imine; (b) hydrolyzing the imine to form a primary amine; and (c) treating the primary amine with a hindered base capable of effecting acyl migration to form another taxane molecule. The Examiner admits the '807 patent teaches a taxane molecule including a protecting group that is removed during a reaction step but does not migrate to another position on the taxane molecule to forma another taxane molecule. Accordingly, the '807 patent does not teach each and every aspect of claim 40.

Despite the admission that the '807 patent does not teach each and every aspect of claim 40, the Examiner argues the anticipation rejection should be maintained because there is allegedly no difference in the definitions of R and R_N. Claim 40 nowhere references R or R_N. Thus, the definitions of R and R_N have no bearing on the rejection of claim 40 under §102(b).

The Examiner goes on to argue it is unclear where the taxane molecule was deprotected and alleges that deprotection must have occurred at the 2' position somewhere in the reaction process. Again, Applicants respectfully point out that claim 40 nowhere recites a "2' position", and a rejection under 35 U.S.C. §102(b) cannot be supported by alleging lack of clarity.

The Examiner is alleging anticipation of claim 40 by a reference that admittedly does not disclose each and every aspect of the claim by attempting to bring extraneous matter into the claim. Applicants respectfully submit that where a reference fails to teach or suggest each and

every aspect of the claims, as is admittedly the case here, a rejection under 35 U.S.C. §102(b) cannot stand, and it certainly cannot be proffered by arguments related to non-claimed matter. As the '807 patent plainly fails to teach or suggest each and every aspect of claim 40, Applicants submit the claim is not anticipated by the cited reference, and Applicants respectfully request reconsideration and withdrawal of the present rejection.

Rejections Under 35 U.S.C. §103(a)

Claims 1-43 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the '807 patent and U.S. Patent No. 5,808,113 (collectively Murray *et al.*). Applicants respectfully traverse this rejection.

The Examiner argues the present rejection is maintained for the reasons of record. In the Office Action dated December 6, 2005, the Examiner alleged the "difference between the instant claims and the prior art process is that Murray does not teach the specific protecting group in C-2' on the figures" (page 4 of the Office Action). The Examiner further argued a skilled artisan "would have been motivated to modify the process of Murray *et al.* by changing one protecting group for another protecting group" (page 4 of the Office Action). Applicants respectfully disagree.

The '807 patent teaches a method for converting protected starting materials (particularly pointing to Figure 4). See, generally, column 4 (line 59) through column 5 (line 4). In Figure 4, a protected amide is converted to a protected imine, which is deprotected through acid hydrolysis or through a separate deprotecting step (see column 5, lines 62-66). The primary amine is then obtained by neutralizing the solution of deprotected molecules. The amine can be converted to Taxol or docetaxel using known techniques (column 6, lines7-21).

The presently claimed methods comprise multiple reaction steps not disclosed by Murray *et al.* These differences easily transcend a difference in C2' protecting groups.

Claim 1 recites a method of converting a taxane molecule according to a defined formula, wherein C2' has an acyl group attached thereto and C3' has an amide group attached thereto. The method comprises: (a) reductively deoxygenating the C3' amide group to form a C3' imine; (b) hydrolyzing the C3' imine to form a C3' amine; and (c) treating the compound with a hindered base capable of effecting acyl migration to form another taxane where the group

previously present on C2' has migrated to C3'. Murray *et al.* do not teach or suggest a step whereby an acyl group migrates from one position to another. Further, Murray *et al.* do not teach a method whereby a protecting group remains throughout the reaction scheme only to be transferred to another site in the final reaction step. Rather, Murray *et al.* teach removing the protecting group prior to forming an amine compound.

The Examiner has pointed to nothing in Murray *et al.* that teaches or suggests keeping the protecting group past formation of an amide. Applicants respectfully direct the Examiner to column 5 (lines 53-66) of the '807 patent, which teaches the protected imines can be converted to the primary amine through acid hydrolysis, such as by using aqueous HCl. The '807 patent goes on to disclose that, "in addition to hydrolyzing the imine, the use of HCl may also remove triethylsilyl protecting groups. However, when other protecting groups and acids are used, it may be necessary to remove the protecting groups separately." Accordingly, the '807 patent clearly teaches steps should be taken to deprotect the imine prior to forming the amine. The deprotecting step is specifically included in the reaction scheme of Figure 4. The Examiner, however, has pointed to nothing in Murray *et al.* teaching or suggesting preserving the protecting group.

Moreover, the Examiner has certainly pointed to nothing in Murray *et al.* teaching or suggesting a migration step. Rather, Murray *et al.* teach removing any group that may migrate by acid hydrolysis or another specific deprotecting step. Accordingly, Applicants respectfully submit the Examiner has failed to point to any portion of Murray *et al.* motivating a skilled artisan to modify the teachings thereof to arrive at the presently claimed invention.

In the present Office Action, the Examiner alleges there is no difference between R and R_N. Applicants respectfully submit the definitions of R and R_N are inconsequential. As noted above, Murray *et al.* fail to teach or suggest maintenance of a protecting group on C2' through formation of an amine. Moreover, Murray *et al.* fail to teach or suggest migrating a substituent from one position to another. In claim 1, the starting molecule is different from the ending molecule. Moreover, the ending molecule is different from the amine formed by Murray *et al.* Still further, the present claims form the ending molecule through a series of steps not taught or suggested by Murray *et al.*

The Examiner again bases the arguments on the mistaken position that the taxane molecule is deprotected. Such is simply not the case in the present claims. The group for migration functions as a protecting group until the migration step; however, there is not a deprotecting step, as disclosed by Murray *et al.* In Murray *et al.*, the end product is the amine, and protection is only required through the deoxygenation step. In the present claims, the protecting group performs two functions – it acts as a protecting group during deoxygenation, but it ultimately acts as the group to be attached to the amino group on the 3' carbon (*i.e.*, the migration step). Murray *et al.* nowhere teach or suggest such a multiple function for the protecting group and nowhere teach or suggest method steps whereby a protecting on the 2' carbon can be transferred to the 3' carbon. Murray *et al.* are clearly distinguishable from the present claims, and the Examiner has pointed to nothing therein that would motivate the skilled artisan to alter the references to achieve the presently claimed method. In fact, the Examiner has pointed to nothing in Murray *et al.* that would even achieve the results obtained by the presently claimed method. Accordingly, Applicants respectfully submit the present claims are not obvious over Murray *et al.*, and Applicants respectfully request reconsideration and withdrawal of the present rejections.

Claims 1-43 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,760,251 and WO 97/07110 (collectively Gao *et al.*). Applicants respectfully traverse this rejection.

Gao *et al.* fail to teach or suggest the presently claimed method steps. For example, claim 40 recites a method for converting an acyl-protected taxane molecule comprising: (a) reductively deoxygenating an amide group on the taxane molecule to form an imine; (b) hydrolyzing the imine to form a primary amine; and (c) treating the primary amine with a hindered base capable of effecting acyl migration to form another taxane molecule. Applicants again stress that Gao *et al.* do not disclose each of these method steps.

The present claims recite methods of converting a taxane molecule. As such, any prior art cited against the claims must expressly or inherently teach or suggest each and every aspect (*i.e.*, each and every method step) of the claims. In the present case, the Examiner admits Gao *et al.* do not expressly teach or suggest each and every claimed method step. The Examiner has provided no further references teaching or suggesting the method steps not disclosed by Gao *et*

al. Rather, the Examiner broadly alleges the missing steps "inherently should be there," and the Examiner bases this broad allegation on the argument that "the prior art has the same starting material and the same product as claimed". Applicants respectfully submit such a line of reasoning is untenable.

To argue that two processes having the same starting and ending material must inherently have the same process steps is to argue there is only a single possible process for arriving at the ending material. There are many known processes for preparing taxanes. Gao *et al*. (see column 2, lines 19 *et seq*. of the '251 patent) disclose as background what they refer to as "the most practical present routes of semi-synthesis" yet go on to teach their own, different methods of synthesis. Yet, as previously noted, none of the methods of synthesis disclosed by Gao *et al*. include all of the presently claimed steps.

In light of the above, Applicants respectfully submit a broad allegation of inherency is insufficient to show obviousness in the present case. The mere fact that a certain thing may result from a given set of circumstances in not sufficient to show inherency. *In re Robertson*, 169 F.3d 743 (Fed. Cir. 1999). In the present case, the Examiner has pointed to nothing in the art that would indicate the process steps not disclosed by Gao *et al*. would inherently be present therein. To this end, Applicants respectfully point out that, to establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. See MPEP 2112(IV). Applicants respectfully submit such a showing cannot be made in reference to Gao *et al*.

Gao *et al*. teach their method of preparing taxanes and disclose other known methods for preparing taxanes, yet none of the disclosed methods disclose each and every step of the present claims. Despite this clear failure, the Examiner would argue the missing steps are inherent. Applicants respectfully submit, however, that to include all of the presently claimed method steps into the disclosure of Gao *et al*. would require extensive modification of the teaching of Gao *et al*., and the Examiner has certainly shown no motivation in Gao *et al*. to make such a modification.

Clearly stated, Gao *et al*. do not teach or suggest the presently claimed method of converting a taxane molecule. Gao *et al*. teach their own methods and known, prior art methods,

but none of the disclosed methods include each and every aspect of the present claims. An inherency argument simply cannot stand in references, such as Gao *et al.*, wherein multiple alternate methods are provided. A skilled artisan would not be motivated to alter Gao *et al.* to incorporate methods steps nowhere disclosed therein. Furthermore, the starting and ending materials in a method are inconsequential when the recited method steps in the prior art do not teach or suggest the claimed method steps. Accordingly, Applicants respectfully submit the claimed method is not obvious over Gao *et al.*, and Applicants respectfully request reconsideration and withdrawal of the present rejection.

Claims 1-43 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,531,611. Applicants respectfully traverse this rejection.

The Examiner again alleges the '611 patent discloses the same starting material and product as presently claimed and argues the claimed steps in converting the starting material to the product would inherently be present in the '611 patent. Again, Applicants submit such an argument is untenable. The present claims are directed to a method of preparation, and the structure of the starting material and the product are inconsequential.

The Examiner has cited no less than five prior art references teaching methods of preparing taxane derivatives, the references generally teaching different process steps for preparing their taxane derivatives. Under the Examiner's logic, the process steps in each cited should inherently be present in the remaining references. This is clearly not the case.

Again, Applicants respectfully disagree with the Examiner's allegation that the presently claimed method steps would be inherently present in the method of the '611 patent. The Examiner has provided no evidence to support such an allegation, and Applicants submit that absent supporting evidence, the broad allegation alone is insufficient to support an obviousness rejection. Accordingly, Applicants respectfully submit the presently recited claims are not obvious over the '611 patent, and Applicants respectfully request reconsideration and withdrawal of the present rejections.

Applicants respectfully submit that all the claims are in condition for allowance. Accordingly, a Notice of Allowance is respectfully requested in due course. If any minor informalities need to be addressed, the Examiner is directed to contact the undersigned attorney by telephone to facilitate prosecution of this case.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR §1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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